## REMARKS

We thank the Examiner for her consideration of all of the art and the return of all of the initialed PTO-1449 forms. A Fourth Supplemental Information Disclosure Statement is enclosed. Consideration of the documents transmitted thereby is respectfully requested.

Before turning to the substance of the Office Action, a summary of the invention will be helpful.

As the Examiner will recall, the present invention relates to, among other things, assays for the detection and/or quantification of human MDA-modified LDL (malondialdehyde-modified low density lipoprotein) and human OxLDL (oxidized low density lipoprotein) in samples derived from the body fluids or tissues of human beings, the MDA-modified LDL and OxLDL containing at least 60 substituted lysine moieties per apo B 100 (apolipoprotein B 100) moiety. At least one antibody used in the assay has high affinity for human MDA-modified LDL and human OxLDL. "High affinity" means an affinity constant (association constant) of at least about $5 \times 10^8$ $M^{-1}$. (See application, e.g., page 5, lines 14-24.)

The invention satisfies a number of needs, among them, the need for non-invasive tests (i.e., assays) that are highly specific for the analytes of interest (i.e., human MDA-modified LDL and human OxLDL). See application, e.g., page 3, lines 7-23. Other aspects of the invention satisfy other needs, including the need for antibodies that are specific for the analytes of interest and the need for a stable standard (e.g., to be used as calibrator and/or control) for the assays.

We now discuss the paragraphs of the Office Action seriatim.

### Office Action, ¶ 5 – formal matters

The "Related Applications" section of the application, which was added by Preliminary Amendment filed at the time of filing the application, has been updated as suggested by the Examiner to include the 6,727,102 patent number.

Office Action, ¶¶ 6 and 7 – alleged obviousness-type double patenting

The Examiner has rejected all claims for alleged obviousness-type double patenting in view of U. S. Patent No. 6,309,888. That patent, entitled "Detection And Determination Of The Stages Of Coronary Artery Disease," issued in 2001 based on an application filed in 1998. The present application was filed in 2004 but claims priority to an application filed in 1997, which is *earlier* than the filing date of the patent on which the rejection is based. The apparent delay is not attributable to applicants nor could the claims of the present application and of the patent have properly been combined in a single application.

Accordingly, the two-way test for obviousness-type double patenting should be used (*Manual Of Patent Examining Procedure*, § 804 at page 800-22 (8th Ed., Rev. 3, August 2005)). In other words, the issue should be whether the claims of the application are obvious from the claims of the patent AND whether the claims of the patent are obvious from the claims of the application. However, even using just the one-way test (i.e., whether the claims of the application are obvious from the claims of the patent), it is clear the obviousness-type double patenting rejection is improper and should be withdrawn. Claim 1 of the 6,309,888 patent reads as follows (emphasis added):

> 1. A method having a clinically sufficient degree of diagnostic accuracy for detecting the presence of and for distinguishing between or among non-acute and acute stages of coronary army [artery] disease for a human patient from the general population, the non-acute stage of coronary artery disease big [being] either asymptomanic [asymptomatic] coronary artery disease or stable angina and the acute stages of coronary artery disease being unstable angina and acute myocardial infraction, the method comprising performing step (b) and performing at least one of steps (a) and (c):
>
> (a) testing a sample from the patient for a clinically significant pressure of a first marker whose presence above

a predetermined level can indicate with a very high degree of diagnostic accuracy the presence of coronay [coronary] artery disease, the first marker being a first atherogenic protein;

(b) testing a sample from the patient for a clinically significant presence of a second marker whose presence above a predetermined level can indicate with a very high degree of diagnostic accuracy the presence of an acute stage of coronary artery disease, the second marker being a second atherogenic protein; and

(c) testing a sample from the patient for a clinically significant presence of a third marker whose presence above a predetermined level can indicate with a high degree of diagnostic accuracy the presence of acute myocardial infarction, the third maker being a heart protein;

(d) the diagnosis based on the results of step (b) and at least one of steps (a) and (c) being:

(i) the absence of coronary artery disease if none of the first, second, and third markers is present above its respective predetermined level;

(ii) non-acute coronary artery disease if the first marker but neither the second or third marker is present above its respective predetermined level;

(iii) unstable angina if each of the first and second markers but not the third marker is present above its respective predetermined level;

(iv) acute myocardial infarction of atherosclerotic origin if each of the first, second, and third markers is present above its respective predetermined level; and

(v) acute myocardial infarction of non-atherosclerotic orign [origin] if neither of the first and second markers but the third marker is present above its respective predetermined level.

The sole independent claim of the present application (claim 56) reads as follows (emphasis added):

56. An immunological assay for the detection and/or quantification of human MDA-modified LDL (malondialdehyde-modified low density lipoprotein) and human OxLDL (oxidized low density lipoprotein) in a sample derived from the body fluids or tissues of a human being, said assay comprising:

(a) contacting the sample with a first antibody that has high affinity for human MDA-modified LDL and human OxLDL; and

(b) thereafter visualizing and/or quantifying a binding reaction between the first antibody and the-MDA modified LDL and OxLDL present in the sample;

wherein the MDA-modified LDL and OxLDL for which the first antibody has high affinity contain at least 60 substituted lysine moieties per apo B-100 (apolipoprotein B-100) moiety.

The Examiner asserts that the two sets of claims "are not patentably distinct from each other because both ... are drawn to the detection of MDA-modified LDL and human OxLDL in a sample." That is not so. The method of the patent is drawn to the detection of certain broad categories of markers (see patent claim 1, above) and in any case need not detect both MDA-modified LDL and OxLDL. The Examiner also asserts that the patent "detects multiple markers ..., however the measurement of additional markers is encompassed by the single marker method recited in the instant application." Again, that is not so. The instant application is not a "single marker method"; the first antibody used has "high affinity for human

MDA-modified LDL and human OxLDL." Furthermore, the test for double patenting involves considering what is recited in the claims, not what is "recited in the instant application," as alleged by the Examiner. Finally, the Examiner says that "[t]he intended use of the method is not germane to the issue of patentability of the method itself." The Examiner has it backwards: the claims of the patent have an intended use, namely, a clinical component, which is recited as an element and not merely in the preamble (see element (d) of the patent claim 1, above).

As explained in the *Manual Of Patent Examining Procedure*, § 804 at pages 800-11 to 800-12 (8th Ed., Rev. 3, August 2005)):

> There are generally two types of double patenting rejections. One is the "same invention" type double patenting rejection based on 35 U.S.C. 101 which states in the singular that an inventor "may obtain a patent." The second is the "nonstatutory-type" double patenting rejection based on a judicially created doctrine grounded in public policy and which is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinguishing from claims in a first patent.

There would certainly be no "prolongation of the patent term" here (see the two claims 1, above). Detecting two specific analytes in a sample (claim 1 of the application) is nothing like what is recited in claim 1 of the patent.

If the Examiner repeats the obviousness-type double patenting rejection, she is asked to explain in detail the basis for the rejection, including her reasoning.

Office Action, ¶ 8 – alleged anticipation

In ¶ 8 of the Office Action, the Examiner has rejected only claim 56 for alleged anticipation based on Holvoet et al., *Journal of Clinical Investigation*, volume 95, number 6, pages 2611-2619 (June 1995). The rejection is believed to be incorrectly premised, for the following reason.

First, it is axiomatic that "[t]o anticipate, every element and limitation of the claimed invention must be found in a single prior art reference, arranged as in the claim. *Karsten Mfg. Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1383, 58 USPQ2d 1286, 1291 (Fed. Cir. 2001); *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1576, 18 USPQ2d 1001, 1010 (Fed. Cir. 1991)." *Brown v. 3M*, 265 F.3d 1349, 1351, 60 USPQ2d 1375, 1376 (Fed. Cir. 2001).

Second, claim 56 calls for, among other things, "contacting the sample with a first antibody that has high affinity for human MDA-modified LDL and human OxLDL." "High affinity" is defined in the application, as follows.

> As used herein (including the claims), "high affinity" means an affinity constant (association constant) of at least about 5 x $10^8$ $M^{-1}$, desirably at least about 1 x $10^9$ $M^{-1}$, preferably at least about 1 x $10^{10}$ $M^{-1}$, and most preferably of at least about 1 x $10^{11}$ $M^{-1}$. [Application, page 5, lines 14-18 (emphasis added)]

The Examiner asserts that the Holvoet article discloses a method for detecting MDA-modified LDL and "[a] monoclonal antibody (mAb-1H11) which to bind with MDA-modified LDL"; however, the Examiner admits that this antibody binds "to a much lesser extent with OxLDL" (Office Action, ¶ 8 at page 5). In fact, as shown in the application, mAb-1H11 has an affinity constant of 3 x $10^{10}$ $M^{-1}$ with respect to MDA-modified LDL but of less than 1 x $10^6$ $M^{-1}$ with respect to OxLDL (application, page 6, table). Antibody mAb-1H11's affinity for OxLDL is clearly **not** "high affinity" (1 x $10^6$ $M^{-1}$ is far less than the claim's required minimum of "at least about 5 x $10^8$ $M^{-1}$"). The simple fact is that mAb-1H11 does not have anything like the "high affinity" for OxLDL required by the claims. The Holvoet article does not anticipate the claims.

Office Action, ¶ 9 – alleged obviousness

In ¶ 9 of the Office Action, the Examiner has rejected claims 57-71 and 73-74 (but not claims 56 or 72) for alleged obviousness based on the Holvoet article (Holvoet et al., *Journal of Clinical Investigation*, volume 95, number 6, pages 2611-2619

(June 1995)) in view of Daiichi EP 0 484 863 A1 (applicant: Daiichi Pure Chemicals Co.; inventors: Akira Kondo et al.).

The Examiner asserts that the Daiichi application "teach[es] a monoclonal antibody and a sandwich immunoassay for measuring malondialdehyde-modified LDL" (Office Action, page 6). The Examiner also assert that "[t]he preparation of the MDA-modified LDL according to the . . . [Daiichi application] does not differ significantly from the preparation according to the instant invention," that "there is no hint that the two methods could lead to different MDA-modified LDL," and that "[c]onsequently, the antibodies raised against these MDA-modified LDL should also not differ significantly" (Office Action, page 6). The Examiner concludes that "[o]ne of ordinary skill in the art would produce and utilize various competitive antibody constructs . . . to detect MDA-modified LDL and OxLDL in a test sample . . ." (Office Action, page 7). The Examiner asserts that "[o]ne of ordinary skill in the art would have been motivated to do this because . . . [the Daiichi application teaches] that modified-LDL exists in two forms – chemically oxidized LDL by copper ions and MDA" and that "[c]learly a precise measurement of modified forms of LDL would encompass the detection of both forms," citing page 2, lines 24-31, of the Daiichi application (Office Action, page 7).

Applicants vigorously disagree with the Examiner's conclusion that the claims are obvious. The Examiner's assertions are incorrectly premised and the Examiner has not met her burden for making the rejection. The claims are clearly unobvious.

First, the Examiner's conclusion that "the [Daiichi] antibodies raised against these MDA-modified LDL should also not differ significantly [from applicants' antibodies]" is wrong. Putting aside the differences between the methods of preparation of the two MDA-modified LDL, it will immediately be understood by those skilled in the art that even if the same antigen were used by applicants and by Daiichi to immunize host animals and even if the immunization protocol as well as the rest of the procedure were the same for obtaining monoclonal antibodies against that antigen (and there is insufficient information for making any such assertion), there is no reason to expect that Daiichi and applicants would obtain exactly the same antibodies. As those skilled in the art know, numerous different antibodies can be formed against the same antigen

(particularly by different animals) because of the numerous different epitopes that are usually present on an antigen. As those skilled in the art also know, there is no reason to expect that the same two groups of antibodies would be obtained, and there is no reason to expect that a valuable antibody found in one group would be found in the other group. Applicants themselves obtained almost one hundred hybridomas against the MDA-modified LDL they used to elicit the antibodies (application, page 12, lines 3-5). Thus, the Examiner's assertion that "the [Daiichi] antibodies raised against these MDA-modified LDL should also not differ significantly [from applicants' antibodies]" is contrary to the knowledge of those skilled in the art and to applicants' experience. The Examiner's assertion is also contrary to the information contained in the Daiichi document itself, which shows that Daiichi's antibodies are significantly different from applicants'.

In Example 5 of the Daiichi application (one of the examples on which the Examiner relies), Antibody 29209 was immobilized on polystyrene balls and used to try to detect what Daiichi refers to as "human MDA-modified LDL" at various concentrations in BSA-PBS using a sandwich assay, and the results are shown in Figure 6. Example 3 shows the use of that same antibody to try to detect "MDA-modified apo B protein" in "normal human serum," and the results are shown in Figure 4. Careful consideration of those examples, however, shows that there is something wrong with Daiichi's reported work and that the Examiner's argument, which is based on that work, is therefore seriously flawed.

The first thing to keep in mind is that the term "human MDA-modified LDL" is used by Daiichi to refer to a manufactured material and not to refer to actual physiological human MDA-modified LDL (see EP 0 484 863 A1, page 4, Example 1, which example is entitled "Preparation of Human MDA-modified LDL and Reduced Type Human MDA-modified LDL"). In contrast, applicants' claims use the term "human MDA-modified LDL" to refer to actual human MDA-modified LDL and not some artificial manufactured material.

These points bear repeating: (1) the term "human MDA-modified LDL" is used by Daiichi to refer to its manufactured material and not to refer to actual physiological human MDA-modified LDL whereas (2) applicants' claims use the term

"human MDA-modified LDL" to refer to actual human MDA-modified LDL and not some artificial manufactured material. The substance being detected in the examples of EP 0 484 863 A1 labeled as "human MDA-modified LDL" is Daiichi's manufactured material and is not actual physiological human MDA-modified LDL.

In Daiichi EP 0 484 863 A1 Figure 4, which shows the results from its Example 3, three different strips are illustrated. The top strip is for "serum from a healthy person," the middle strip is for "human MDA-modified LDL," and the bottom strip is for "human LDL." (It goes without saying that their separate testing and listing indicates that "serum from a healthy person" and "human MDA-modified LDL" are not the same.)

In Example 3, tests were run using Antibody 29209, and Figure 4 shows four stained bands in the middle strip when Daiichi's manufactured "human MDA-modified LDL" was tested. The top strip, resulting from testing "serum from a healthy person," shows three bands. Most significantly, only one of the bands in the top strip in any way matches (i.e., lines up with) any of the bands in the middle strip. Thus, three of the four bands for Daiichi's manufactured "human MDA-modified LDL" have no corresponding bands in the top strip for "serum from a healthy person," and two of the three bands in the strip for "serum from a healthy person" have no corresponding bands in the results for Daiichi's manufactured "human MDA-modified LDL."

If we accept as true Daiichi's clear representations that the person from whom the serum was taken for Example 3 and Figure 4 was healthy (also referred to by Daiichi as "normal"), Daiichi should not have detected any significant amount of MDA-modified LDL in that person's serum, yet the bands in Figure 4 appear to indicate that significant amounts were present. A truly healthy person is not believed to have any disease-indicating (i.e., clinically significant) amount of MDA-modified LDL present in his or her serum. In fact, the presence of a significant amount of physiological MDA-modified LDL in the blood (serum or plasma) is an indication of acute coronary artery disease, namely, either unstable angina or acute myocardial infarction. See U. S. Patent No. 6,309,888, column 18, line 47 et seq. Accordingly, Daiichi is wrong in stating in Example 3 that it found in the serum of a healthy person MDA-modified apo B protein, that is, MDA-modified LDL (as noted in the present application at page 1, lines 23-24,

apo B-100 is the prominent apolipoprotein in LDL). Whatever Daiichi found in the "serum from a healthy person" (and it presumably did find something because there are three stained bands in the top strip of Figure 4), it was highly unlikely to be actual human (physiological) MDA-modified LDL.

We can look at Daiichi's results another way. If we assume solely for the sake of argument that Daiichi did detect its manufactured "human MDA-modified LDL" (as shown by the four bands in the middle strip of Figure 4) and that this manufactured material would be essentially the same as the actual physiological MDA-modified LDL that would be found in the serum of a person with acute coronary artery disease (i.e., actual human MDA-modified LDL), then what was detected by Daiichi in the human serum as shown in the top strip of Figure 4 could not be physiological MDA-modified LDL, regardless of whether the person was healthy. That is plainly true because the bands of the top strip ("serum . . .") and middle strip ("human MDA-modified LDL) in Figure 4 are so dissimilar. Again, based on Daiichi's own assumptions, whatever Daiichi found in human serum, it was highly unlikely to be actual human (physiological) MDA-modified LDL.

Looking at the Daiichi work yet another way, and again accepting as true Daiichi's representation that the person from whom the serum was taken was healthy, the fact that use of Antibody 29209 produced three bands for "serum from a healthy person" (top strip of Figure 4) but did not produce any bands for "human LDL" (bottom strip of Figure 4) also indicates that there is something wrong with Daiichi's assertion that Antibody 29209 is detecting MDA-modified LDL in normal (healthy) human serum. The results for the top and bottom strips of Figure 4 should have been essentially the same for a healthy person.

The question one might then ask is what Daiichi's antibodies did detect in human serum (top strip of Figure 4). Although one skilled in the art cannot say what was detected (because it simply is not clear), one can say with confidence what was *not* detected, namely, actual physiological human MDA-modified LDL, which is what application claim 1 concerns.

In summary, and assuming for the sake of argument that the Examiner's assertions are correct, if the person whose serum was tested (top strip of Figure 4) was

healthy (as represented by Daiichi to be the case), Antibody 29209 should not have found anything significant in "human serum from a healthy person" (that is, there should have been no stained bands in the top strip of Figure 4 just as there are no stained bands for "human LDL" in the bottom strip of Figure 4). Alternatively, and again assuming for the sake of argument that the Examiner's assertions are correct, if the person was not healthy (i.e., had acute coronary artery disease), Antibody 29209 should have produced the same bands for the serum (top strip of Figure 4) as it produced for "human MDA-modified LDL" (middle strip of Figure 4), but it didn't. Whichever is the true case, the conclusions are the same, namely, that Daiichi's antibodies and assay cannot find true human (actual physiological) MDA-modified LDL in the serum of a human being and the Examiner's assertions are not correct. In great contrast, applicants' antibodies can find true human MDA-modified LDL in the serum of a human being.

There is still another independent reason confirming applicants' reading of the Daiichi application and confirming that the Examiner is wrong. In EP 0 484 863 A1, at page 3, lines 42-43, Daiichi states that its manufactured "[h]uman MDA-modified LDL can be converted into reduced type human MDA-modified LDL by an appropriate reducing treatment to improve its storability" (emphasis added). That is the exact opposite of what applicants found, namely, that their MDA-modified LDL was stable (see application, starting at page 7, line 33). Thus, the present application at page 9, lines 3-4, reads: "It has been found that LDL that has been modified by treatment with MDA is highly stable." This discrepancy (Daiichi's MDA-modified LDL must be treated (reduced) to improve its storability but applicants' MDA-modified LDL is highly stable) is consistent with the conclusions that Daiichi's antibodies and assay cannot find physiological (true human) MDA-modified LDL in the serum of a human being and that the Examiner's assertions are wrong.

The only example of the Daiichi application in which there was any attempt to detect anything not in a completely artificial construct (e.g., the BSA-PBS of Daiichi Example 4), is Example 3, where Antibody 29209 was used. The poor sensitivity of that antibody is evidenced by Daiichi Example 5, on which the Examiner relies.

In Example 5, Antibody 29209 was used to detect Daiichi's manufactured (i.e., non-physiological) "human MDA-modified LDL." (As discussed above, and contrary to the Examiner's belief, it is most unlikely that this antibody could detect in human serum any true human MDA-modified LDL). The Daiichi antibody is substantially less sensitive than the antibodies used by applicants, so even if the Daiichi antibody could detect the right substance (the analyte), it could not do so with the analyte at anywhere near the same low concentrations at which applicants' antibodies can successfully function.

Applicants' antibodies are capable of detecting 0.02 milligrams/deciliter of human (physiological) MDA-modified LDL in undiluted human plasma. Ignoring the differences between undiluted human plasma, with all of its many components that make detection more difficult, and the simple artificial BSA-PBS composition used by Daiichi in Example 5, which makes it easier for Daiichi to detect its manufactured "human MDA-modified LDL," Figure 6 shows that the Daiichi assay is totally insensitive to any change in antigen concentration below a level several times higher than applicants' 0.02 mg/dl value.

More specifically, applicants' 0.02 milligrams/deciliter is equal to 0.2 micrograms/milliliter (micrograms/milliliter are the units used for the abscissa of EP 0 484 863 A1 Figure 6), and in Figure 6 the absorbance remains essentially minimal (at a background "noise" level) until a concentration of nearly 1 microgram/milliliter is reached, five times the 0.2 micrograms/milliliter level. Antibody 29209 (and not Antibody 29210) is clearly Daiichi's preferred antibody for trying to detect physiological MDA-modified LDL, since that is the antibody Daiichi used in Example 3, the only example in which actual human serum was used and an example Daiichi ran to try to "confirm" the presence of MDA-modified LDL in normal human serum (see, e.g., the title of Example 3).[1] Simply put, Daiichi's antibodies and assays are not anywhere near

[1] The Examiner points to Antibody 29210 in Example 4 of the Daiichi application and asserts that Antibody 29210 has a "detection limit of less than 0.01 mg/dl MDA-modified LDL in an ELISA" (Official Action, page 7). However, Antibody 29210 was tested against Daiichi's manufactured "human MDA-modified LDL," not against true human (physiological) MDA-modified LDL, and it was tested in BSA-PBS, not in undiluted human plasma. Note the use in applicants' claims of "sample derived from the body fluids or tissues of a human being" (e.g., claim 56), "human MDA-modified LDL" (e.g., claim 56), and

*[footnote cont'd ...]*

applicants' and the Examiner's assertions (e.g., that the antibodies are the same) are wrong.

It should be abundantly clear that there is no way to combine the Holvoet article and the Daiichi application to achieve applicants' claimed invention, which involves, among other things, the detection and/or quantification of human MDA-modified LDL and human OxLDL in a sample derived from the body fluids or tissues of a human being by contacting the sample with an antibody that has high affinity for human MDA-modified LDL and human OxLDL. Despite that, after discussing Daiichi's non-physiological manufactured "human MDA-modified LDL" at length and with nary a mention of OxLDL, the Examiner suddenly asserts that "[t]herefore" (i.e., in view of the Daiichi application and the Holvoet article), one skilled in the art would "produce and utilize various comparative antibody constructs . . . to detect MDA-modified LDL and OxLDL" (Office Action, page 7).

Merely noting the existence of "chemically oxidized LDL" (EP 0 484 863, page 2, line 25) does not by magic convert Daiichi's antibodies into ones capable of finding that substance as the Examiner seems to suggest (Office Action, page 7): one can be highly "motivated" and still not have antibodies that can find both MDA-modified LDL and OxLDL.

**As should be obvious, (1) there is no mention of *detecting* human OxLDL in either the Daiichi application or the Holvoet article and, thus, (2) the Examiner's conclusion comes out of the blue, without any sound basis.**

Applicants fail to understand how the Holvoet article and/or the Daiichi application in any way suggest an assay that, among other things, can detect and/or quantify human MDA-modified LDL and human OxLDL using an antibody that has high

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*[...footnote cont'd]*

"undiluted human plasma" (claim 74). Thus, claim 56 specifies that human (i.e., physiological) MDA-modified LDL (and not Daiichi's manufactured and misleadingly named "human MDA-modified LDL") is being detected and/or quantified in a sample derived from the body fluids or tissues of a human being. Furthermore, the Examiner has adduced no evidence that Daiichi's antibodies have "high affinity" for true human MDA-modified LDL as required by the claims, particularly given how "high affinity" is defined in the application (see page 5, lines 14-24). In fact, from the foregoing discussion, it should be clear that there is no good evidence in EP 0 484 863 A1 that Daiichi's antibodies have high affinity for true human (physiological) MDA-modified LDL in any sample, whether or not derived from the body fluids or tissues of a human being.

affinity for both. Certainly the Holvoet article does not suggest that. As to the Daiichi application, all one of ordinary skill in the art need do is read any part of that application (e.g., its title, its abstract, its field of the invention, its summary of the invention, its brief description of the drawings, its detailed description of the invention, including the examples, or its claims) to be firmly convinced that the Daiichi application has nothing whatsoever to do with detecting and/or quantifying OxLDL and that the Examiner's suggestion to the contrary is ill-founded. For example, the title of the Daiichi application is "A monoclonal antibody and a method for measuring malondialdehyde-reacted low-density lipoproteins."

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It is readily apparent that the Examiner has not met her burden for making a prima facie case for obviousness. Section 706.02(j) of the *Manual Of Patent Examining Procedure* (8th Ed., Rev. 3, August 2005)) reads in part as follows (underlining added; italics in original):

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. . . .
>
> The initial burden is on the examiner to provide some suggestion of the desirability of doing what the inventor has done. "To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or

> the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." . . .

*In re Dembiczak*, 50 USPQ2d 1614, 1616-17 (Fed. Cir. 1999), sets forth the law concerning the first of the three requirements (namely, the need for there to be evidence in the prior art, and not in applicants' disclosure, of a suggestion or motivation to modify or combine the reference teachings):

> Our analysis begins in the text of section 103 quoted above, with the phrase "at the time the invention was made." For it is this phrase that guards against entry into the "tempting but forbidden zone of hindsight" . . . , when analyzing the patentability of claims pursuant to that section. Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. . . .
>
> Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. . . . *In re Rouffet*, 149 F.3d 1350, 1359, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998) ("the Board must identify specifically . . . the reasons one of ordinary skill in the art would have been motivated to select the references and combine them"); *In re Fritch*, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992) (examiner can satisfy burden of obviousness in light of combination "only by showing some objective teaching

[leading to the combination]"); *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) (evidence of teaching or suggestion "essential" to avoid hindsight); *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 297, 227 USPQ 657, 667 (Fed. Cir. 1985) (district court's conclusion of obviousness was error when it "did not elucidate any factual teachings, suggestions or incentives from this prior art that showed the propriety of combination"). See also *Graham*, 383 U.S. at 18, 148 USPQ at 467 ("strict observance" of factual predicates to obviousness conclusion required). Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability – the essence of hindsight. See, e.g., *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138, 227 USPQ 543, 547 (Fed. Cir. 1985) ("The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time.").

. . .

We have noted that evidence of a suggestion, teaching, or motivation to combine may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved . . . , although "the suggestion more often comes from the teachings of the pertinent references" . . . . The range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular. . . . Broad conclusory statements regarding the teaching of multiple references, standing alone, are not "evidence." . . . [Emphasis added; some citations omitted; bracketed text in original]

With these principles in mind, we review the Examiner's prima facie case for obviousness.

- **There Is No Evidence Of A Suggestion Or Motivation To Combine**

The best the Examiner can do to find the required suggestion or motivation to combine the Holvoet article and the Daiichi application is to assert that the Daiichi application teaches at page 2 "that modified-LDL exists in two forms – chemically oxidized LDL by copper ions and MDA" and that "[c]learly a precise measurement of modified forms of LDL would encompass the detection of both forms" (Office Action, page 7). As noted above, the only mention of oxidized LDL in the Daiichi application is at page 2, lines 24-31, and careful reading of the Daiichi application and the brief section in it cited by the Examiner (EP 0 484 863 A1, page 2, lines 24-31) shows that it is not in any way even a *hint* that anyone look for human OxLDL using the Daiichi antibodies. In fact, Daiichi's silence on using its antibodies to detect any OxLDL (human or manufactured) is certainly proof that its antibodies cannot do so (see Daiichi EP 0 484 863 A1, page 2, lines 40-50).

The Examiner's "rationale" for making the combination is precisely the sort of rationale that the Court of Appeals for the Federal Circuit has consistently held to be insufficient. The Examiner's rationale contains absolutely no reference to any real evidence in the prior art (see, e.g., Section 706.02(j) of the *Manual Of Patent Examining Procedure*, quoted above). As noted in *Dembiczak*, above, the "examiner can satisfy burden of obviousness in light of combination 'only by showing some objective teaching [leading to the combination].'" Where is there any "objective teaching" in the Examiner's rationale? There isn't any. As also noted in *Dembiczak*,

> The range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular. . . . Broad conclusory statements regarding the teaching of multiple references, standing alone, are not "evidence." [emphasis added]

Where is there any "actual evidence"? There isn't any. Where is there any actual evidence that is "clear and particular"? There isn't any. However, what there is in the

Examiner's rationale is a "broad conclusory statement[]," which the Court of Appeals for the Federal Circuit says is "not evidence.'"

The Examiner is in essence attempting to use applicants' own teachings about their invention against applicants. In doing so, the Examiner has violated Section 706.02(j) of the *Manual Of Patent Examining Procedure*, quoted above: "The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure."

- **There Is No Evidence Of A Reasonable Expectation Of Success**

Regarding the second requirement of Section 706.02(j) of the *Manual Of Patent Examining Procedure* for making a case of prima facie obviousness (namely, the need for there to be evidence in the prior art, and not in applicants' disclosure, of a reasonable expectation of success flowing from modifying or combining the art), the Examiner has not really addressed this point. In other words, the Examiner has not indicated why one skilled in the art would think that any combination of the Holvoet article and the Daiichi application would produce applicants' claim invention, which requires, among other things, contacting the sample derived from the body fluids or tissues of a human being with a first antibody that has high affinity for human MDA-modified LDL and human OxLDL. Thus, for example, for reasons discussed above, the Examiner has adduced no good evidence that the Daiichi antibodies have the required "high affinity" for true human MDA-modified LDL, let alone for true human OxLDL, nor that they can detect those substances in an actual physiological sample and not some artificial construct. Furthermore, the Examiner has adduced no good evidence that anyone skilled in the art would think that any combination of Holvoet and Daiichi would yield an assay that can find human MDA-modified LDL and human OxLDL.

There simply is no evidence of a "reasonable expectation of success . . . [to] be found in the prior art and not based on applicant's disclosure" as required by Section 706.02(j) of the *Manual Of Patent Examining Procedure*.

- **The Examiner Has Not Demonstrated How The Cited Art Teaches Or Suggests All The Claim Limitations**

Regarding the third and final requirement of Section 706.02(j) of the *Manual Of Patent Examining Procedure* for making a case of prima facie obviousness (namely, the need to show that the cited art teaches or suggests all the claim limitations), the Examiner has not met her burden. For example, where is there in the Office Action any showing that the cited art teaches or suggests a method having the limitations of, for example, claim 56? In other words, where is there any showing that any combination of the cited art yields an assay involving "contacting the sample with a first antibody that has **high affinity** for **human** MDA-modified LDL **and human** OxLDL"?

## CONCLUSION

Favorable action on the merits, including allowance of all the claims, is respectfully requested.

If the Examiner has any questions regarding this paper, she is respectfully requested to telephone the undersigned attorney if doing so would expedite prosecution of this case.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Mail Stop Amendment, Commissioner For Patents, P.O. Box 1450, Alexandria, VA 22313-1450

on May 30, 2006
(Date of Deposit)

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Respectfully submitted,

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